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Original Article

Plasma renin levels and renin–blood pressure relationship in normal-weight and overweight children with obstructive sleep apnea and matched controls

Abu Shamsuzzaman *, Rhonda D. Szczesniak, Matthew C. Fenchel, Raouf S. Amin

Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

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ABSTRACT

Background: Obstructive sleep apnea (OSA) has been increasingly linked to elevated blood pressure (BP) and hypertension. Repeated night-time hypoxia in OSA is associated with activation of two critical mechanisms of BP control: the autonomic nervous system and the renin–angiotensin system (RAS). The effects of OSA on the RAS are not well understood, especially in children. We hypothesized that children with OSA have elevated renin levels and abnormal relationships between BP and renin.

Methods: Polysomnography was conducted in 173 children to diagnose OSA (apnea–hypopnea index [AHI] >1 event/h) and control (AHI ≤1 event/h) groups. Age- and gender-specific *z*-scores for body mass index (BMI) were calculated to divide subjects into obese (BMI ≥95%), overweight (BMI ≥85% and <95%) and normal-weight (BMI <85%) groups. Morning BP was measured with an automatic sphygmomanometer and venous blood samples were collected for measurements of plasma renin, after overnight polysomnography.

Results: Plasma renin levels were not significantly different in all four groups after adjustment of age, gender, and race. Significantly negative associations between renin and BP were present only in the normal-weight control group and were absent in the other three groups.

Conclusion: Plasma renin levels were not significantly increased in children with OSA compared to controls for both normal-weight and overweight subjects. The absence of normal, negative renin–BP relationships in both overweight and OSA children suggests a dysfunction of the RAS, which could be a mechanism for increased BP and the development of hypertension.

1. Introduction

Obstructive sleep apnea (OSA) has been increasingly linked to cardiovascular diseases [1]. In children with OSA, blood pressure (BP) is elevated not only during sleep apnea events at night, but also during daytime wakefulness while breathing normally [2–5]. Hypertension [6] and drug-resistant hypertension [7] are widespread in the middle-aged adult population with OSA. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identified OSA as the most prevalent among identifiable causes of hypertension [8]. Experimental animal models of OSA have a significant increase in BP that is normalized after elimination of OSA [9]. In clinical studies, successful treatment of OSA significantly reduced BP in hypertensive patients with OSA [10–13]. These studies provide compelling evidence of a causal relationship between OSA and hypertension. However, the pathophysiologic mechanism of elevated BP and mechanisms for the development of hypertension in OSA patients are poorly understood.

Repeated night-time apneic events during sleep in OSA patients are associated with hypoxemia and frequent arousals that cause sleep disturbance and sleep fragmentation [14]. Hypoxemia and partial sleep loss in OSA patients are strongly associated with sympathetic neural activation [15], oxidative stress [16], inflammation [17], coagulation [18], endothelial dysfunction [19], and metabolic and hormonal dysregulation [20,21]. Markedly elevated sympathetic activity in patients with OSA is a well-recognized mechanism of increased BP that may cause development of neurogenic hypertension [22]. Recently published results of reduced baroreflex sensitivity [23] and impaired BP control [24] in children with OSA suggest an abnormality in the neural feedback regulation of BP that causes increased BP in children with OSA. Baroreflex dysfunction in these children may be a critical mechanism of increased BP, considering the significant improvement of baroreflex sensitivity after treatment of OSA with adenotonsillectomy [25].

* Corresponding author at: Divisions of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229, USA. Tel.: +1 513 803 0376; fax: +1 513 636 4615.
E-mail address: Abu.Shamsuzzaman@CCHMC.org (A. Shamsuzzaman).

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The renin–angiotensin system (RAS) plays an important role in long-term BP regulation through maintenance of the extracellular fluid volume as a vasoconstrictor. Dysregulation of either the sympathetic nervous system or the RAS, or a combination of both, contributes to BP elevation and the development of hypertension. Although extensive data are available on the sympathetic mechanism of BP regulation in OSA [15], data on the RAS in adult patients with OSA are limited, and, to our knowledge, no data are available in children with OSA. Further, the results of previous studies on the RAS in adult OSA patients are controversial. Increased angiotensin II [26] and similar levels of renin and aldosterone [27,28] have been reported in OSA patients compared to matched controls. A significantly positive relationship between severity of OSA and plasma aldosterone in patients with resistant hypertension has also been reported [29]. The levels of plasma renin are associated with age [30], gender [31], obesity [32], sleep cycle [33], time of the day [34], and dietary salt intake [35]. Although obesity is an important risk factor for OSA, the effects of obesity on renin levels in children with OSA have not been studied. In normotensive children, plasma renin and aldosterone levels are negatively related to ambulatory BP measurements [36].

The present study aimed to examine the levels of plasma renin and their association with BP both in children with OSA and in healthy children who were either overweight or normal weight. We tested the hypothesis that OSA children, whether overweight or normal weight, would have increased plasma renin levels compared to their respective control groups matched for age, gender, and race and an altered negative association between BP and renin.

2. Methods

2.1. Subjects

Children aged 5–14 years were recruited from the Otolaryngology and Pediatric Clinic of Cincinnati Children's Hospital Medical Center for overnight polysomnography (PSG) for diagnosis of OSA. Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Age- and gender-specific *z*-scores for body mass index (BMI) were calculated using reference data available in the Centers for Disease Control and Prevention 2000 growth charts for the USA [37]. Children with OSA were divided by BMI percentile into normal-weight (BMI <85%), overweight (BMI ≥85% and <95%) and obese (BMI ≥95%) groups. Healthy control children (without OSA) matched for age, gender, race, and BMI percentile were also recruited for PSG. OSA subjects were free of cardiovascular, cerebrovascular, and any chronic medical disorders or genetic conditions, had never been treated for OSA, and either were on no medications or chronic asthma medications were temporarily discontinued for ≥24 h prior to the sleep study. Control subjects were free of any acute or chronic disease and on no medications. Signed informed consent and assent for children aged >7 years were obtained from each study participant before enrollment in the study. The study was approved by the Cincinnati Children's Hospital Medical Center Institutional Human Subjects Review Board.

2.2. Study design

A medical history was obtained and a physical examination was performed on all subjects before the sleep study. The presence and severity of OSA were determined by standard overnight PSG, including electroencephalography, electro-oculography, electromyography, finger-pulse oximetry, thermistor measurements of oronasal airflow, and measurements of rib-cage and abdominal movements of breathing. The presence of snoring was identified with recording of audio and vibration using a microphone taped on the throat of the subjects. All sleep studies were scored according to the standard criteria set by the American Thoracic Society and by the same board-certified sleep specialist.

Demographic data, heart rate, and BP were measured in the evening prior to the sleep study. All subjects awakened spontaneously in the early morning, and blood samples were collected and BP was measured while the subjects were on the bed in a supine position and prior to ambulation. Venous blood was collected for measurements of renin levels immediately after awakening. Supine BP was measured three times in the morning after the blood draw with an automatic sphygmomanometer (Dinamap; Critikon, Tampa, FL, USA), and averages of the three BP measurements were used for the statistical analyses.

2.3. Renin analysis

Plasma renin levels were determined by an immunoradiometric assay using Packard Cobra II Auto-Gamma Counter Model D5005 (Hewlett Packard, Meriden, CT, USA). In brief, a primary monoclonal antibody recognizing both the active and inactive forms of renin was used, followed by a secondary antibody labeled with ^{125}I that specifically recognizes the active form of renin. The assay involved the incubation of both standard (calibrated against the international reference preparation: WHO 68/356) and unknown sera in the presence of an excess of the first insolubilized antibody on the wall of polystyrene tubes followed by an excess of the second antibody. After a 3 h room-temperature incubation, the tubes were washed to remove unbound material to the solid phase. The amount of complex, bound radioactivity was measured in a gamma-counter. Results of the samples were determined directly from the standard curve. Sensitivity of the analysis was 1 pg/mL. Intra-assay variations were 3.6% for low sample and 1.8% for high sample. Inter-assay variations were 5.0% for low sample and 3.7% for high sample. Ranges of measurements were between 1 and 320 pg/mL.

2.4. Statistical analysis

Descriptive analyses were performed with calculation of means, standard deviations, and medians for continuous variables. Categorical variables were measured using proportions. Bivariate associations of continuous renin and BP variables (systolic, diastolic, and mean BP) were analyzed using Spearman correlation coefficients. An analysis of covariance model was used to compare groups for differences in renin levels (log-transformed) and morning values for diastolic, systolic, and mean BP. Age, gender, and race were included as covariates. Least-squares means were compared between groups of interest, using a multiple comparison adjustment based on simulation. Significance was set a priori at $\alpha = 0.05$. Analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Demography, hemodynamics, and sleep profile in OSA and control subjects

Demography, hemodynamics, and sleep profile were not significantly different in OSA and control for both normal-weight and overweight groups, except for arousal index (AI), respiratory disturbance index (RDI), apnea–hypopnea index (AHI), and percent of REM sleep (Table 1). In overweight children, AI, RDI, and AHI were significantly increased in OSA compared to control subjects. In normal-weight children, percent of REM sleep, RDI, and AHI were significantly increased in OSA compared to control subjects.

Table 1
Comparison of demographics, hemodynamics, and sleep profile for both normal-weight and overweight control and OSA subjects.

	Normal-weight control ($n = 52$)	Normal-weight OSA ($n = 47$)	Overweight control ($n = 27$)	Overweight OSA ($n = 47$)
Gender (female:male)	27:25	26:21	14:13	34:13
Age range (years)	5.4–14.3	4.1–13.9	6.1–14.2	5.1–14.3
Age (years)	9.4 ± 2.7	8.6 ± 3.0	10.7 ± 2.3[a]	9.8 ± 2.5[b]
Race (Caucasian:others)	35:17	30:17	18:9	26:21
BMI (kg/m^2)	17.2 ± 1.9	17.8 ± 6.8	24.3 ± 4.3[a]	24.4 ± 4.6[b]
BMI *z*-score	0.2 ± 0.6	0.1 ± 0.8	1.7 ± 0.4[a]	1.8 ± 0.4[b]
Systolic BP (mmHg)	105 ± 1.3	105 ± 1.3	114 ± 1.8[a]	110 ± 1.3[b]
Diastolic BP (mmHg)	60 ± 0.8	59 ± 0.9	64 ± 1.2[a]	61 ± 0.9
Mean BP (mmHg)	76 ± 1.0	75 ± 1.1	82 ± 1.5[a]	79 ± 1.1[b]
Total sleep time (min)	523 ± 41	531 ± 42	539 ± 31	534 ± 40
Sleep efficiency (%)	80 ± 12	78 ± 11	78 ± 13	75 ± 12
Sleep latency (min)	54 ± 48	63 ± 45	53 ± 40	64 ± 47
REM latency (min)	185 ± 71	171 ± 67	157 ± 67	183 ± 76
Stage 1 sleep (%)	3 ± 1	3 ± 1	3 ± 1	3 ± 1
Stage 2 sleep (%)	46 ± 8	46 ± 8	48 ± 8	48 ± 6
Slow wave sleep (%)	31 ± 7	29 ± 7	28 ± 8	29 ± 5
REM sleep (%)	20 ± 5	22 ± 5[c]	21 ± 4	20 ± 4[b]
AI (events/h)	10.4 ± 3.0	12.4 ± 5.7	8.1 ± 2.5[a]	14.3 ± 8.9[d]
RDI (events/h)	1.0 ± 1.5	7.7 ± 8.3[c]	0.7 ± 0.4	7.9 ± 6.5[d]
AHI (events/h)	0.3 ± 0.3	6.9 ± 8.4[c]	0.5 ± 0.4[a]	7.3 ± 36.5[d]
REM SpO_2 (%)	97 ± 2	97 ± 1	98 ± 1	98 ± 1
Non-REM SpO_2 (%)	97 ± 1	97 ± 1	97 ± 1	97 ± 1
Renin (pg/mL)	12.3 (10.8–13.9)	13.3 (11.6–15.3)	12.3 (10.2–14.7)	14.3 (12.5–16.4)

OSA, obstructive sleep apnea; BMI, body mass index; BP, blood pressure; REM, rapid eye movement; AI, arousal index; AHI, apnea hypopnea index; RDI, respiratory disturbance index; SpO_2, oxygen saturation.
Values are mean ± SD or median (range).
[a] $P < 0.05$, normal-weight control vs overweight control.
[b] $P < 0.05$, normal-weight OSA vs overweight OSA.
[c] $P < 0.05$, normal-weight control vs normal-weight OSA.
[d] $P < 0.05$, overweight control vs overweight OSA.

3.2. Plasma renin in OSA and control subjects

Least-squares estimates of log-transformed renin levels were not significantly different between OSA and control subjects in both normal-weight and overweight groups after adjustment for age, gender, race, and diastolic BP (Fig. 1). In addition, plasma renin levels were not significantly different between normal-weight and overweight subjects in both control and OSA groups after adjustment for age, gender, race, and diastolic BP (Fig. 2).

3.3. Effects of obesity on plasma renin in OSA and control subjects

Renin levels were compared between OSA and control in normal-weight (BMI ≤85th percentile), overweight (BMI >85th and <95th percentile), and obese (BMI ≥95th percentile) subjects. Plasma renin levels were not significantly different between OSA and control subjects in normal-weight, overweight, and obese groups after adjustment for age, gender, and race (Fig. 3). Additionally, levels of obesity had no significant effects on renin levels in OSA or control subjects.

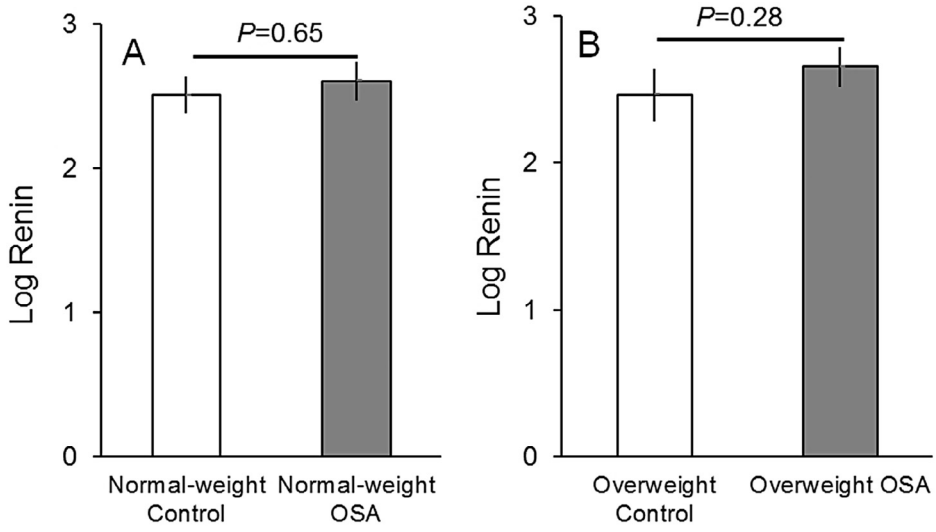

Fig. 1. Renin levels in control and obstructive sleep apnea (OSA) subjects for normal-weight (A) and overweight (B) subjects after adjustment for age, gender, race, and diastolic blood pressure. Values are least-squares estimates of log-transformed renin levels with upper and lower confidence intervals.

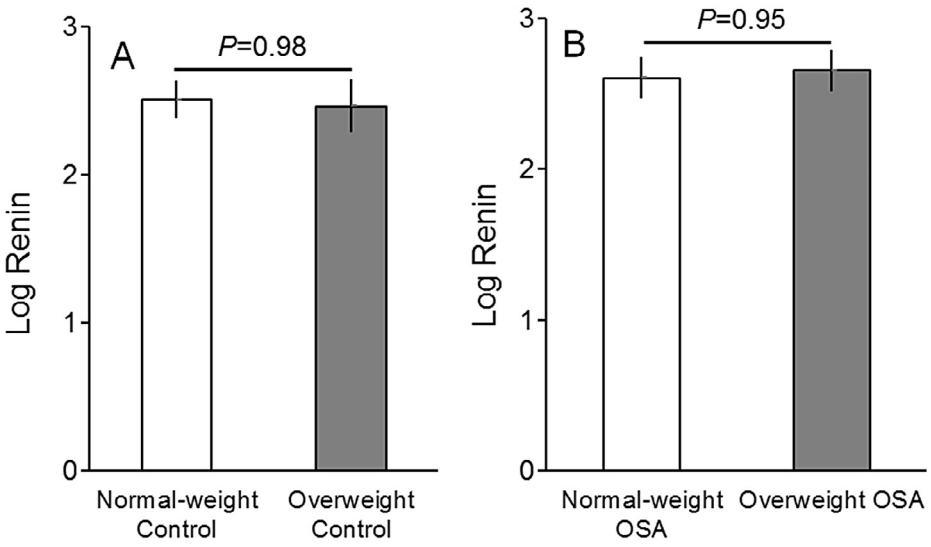

Fig. 2. Renin levels in normal-weight and overweight control (A) and obstructive sleep apnea (OSA) (B) subjects after adjustment for age, gender, race, and diastolic blood pressure. Values are least-squares estimates of log-transformed renin levels with upper and lower confidence intervals.

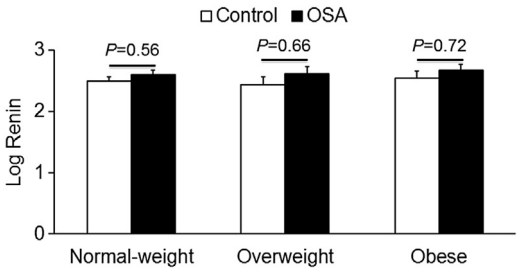

Fig. 3. Renin levels in control and obstructive sleep apnea (OSA) normal-weight [body mass index (BMI) ≤ 85th percentile], overweight (BMI >85th and <95th percentile) and obese (BMI ≥95th percentile) subjects after adjustment for age, gender, race, and diastolic blood pressure. Results are least-squares estimates of log-transformed renin levels with standard errors of the means.

3.4. Correlations between BP and renin levels

Correlation analyses were conducted to determine relationships between renin levels and early morning BP, including systolic, diastolic, and mean BP. There were significantly negative correlations between renin and BP in normal-weight control subjects (Fig. 4). However, there was no association between renin level and BP in overweight control, normal-weight OSA, and overweight OSA groups. Further stratifying the cohort into normal-weight and overweight groups revealed a significantly negative association between renin level and BP in normal-weight control subjects only, but not in normal-weight OSA subjects. In overweight subjects, there were no significant associations between renin level and BP in both the control and OSA groups. Additional subgroup analyses in OSA subjects with AHI ≤5 and >5 events/h did not indicate statistically

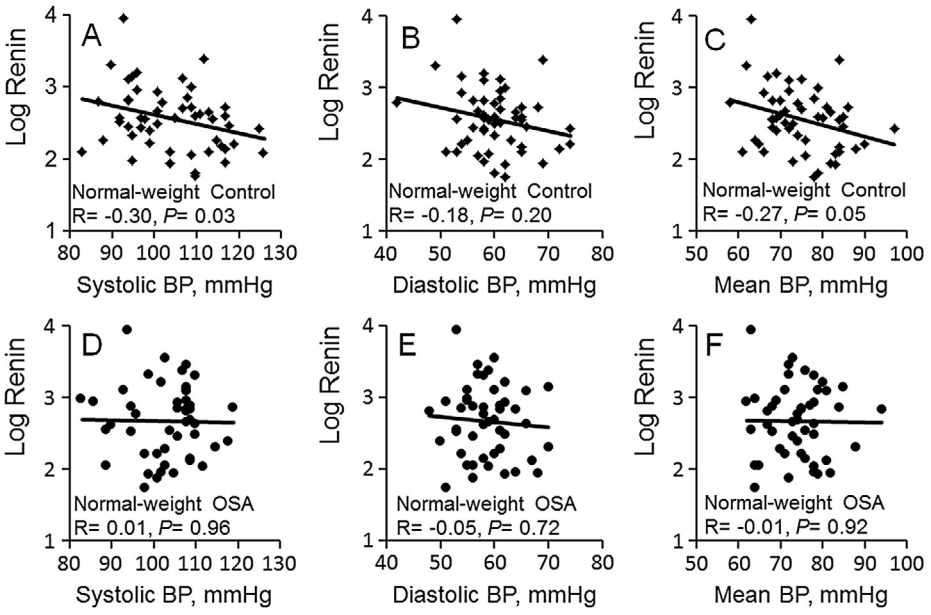

Fig. 4. Relationship between blood pressure (BP; systolic, diastolic, or mean) and renin levels in normal-weight control (A–C) and normal-weight obstructive sleep apnea (OSA) (D–F) subjects. *R*, Pearson correlation coefficient.

significant differences between renin and BP values (systolic, diastolic, or mean).

4. Discussion

Our findings demonstrate that normal-weight children, with or without OSA, have similar renin levels, and that elevated renin levels in overweight children with OSA compared to overweight control subjects are not statistically significant ($P = 0.28$; Fig. 1). The normal negative association between renin level and BP only was present in normal-weight control subjects. Therefore, the absence of the negative association between renin level and BP in children with OSA and in overweight children suggests that both obesity and OSA significantly affect the RAS-mediated control of BP. Dysfunction of the RAS-mediated feedback control of BP may be a potential mechanism for elevated BP and thus development of hypertension and resistant hypertension in children with OSA, particularly in overweight and obese individuals.

The RAS is a critical mechanism for BP regulation. The role of the RAS for development of cardiovascular diseases including hypertension is well established [38]. Previous studies on RAS in OSA patients were inconsistent, with both increased and similar renin levels described [26–28], possibly associated with small sample sizes. Factors associated with elevated plasma renin levels are decreased renal afferent arteriolar pressure, increased renal sympathetic drive, and decreased sodium chloride in the macula densa. In a resting supine condition, levels of plasma renin vary depending on the time of the day [39]. The presence of comorbid conditions including obesity and hypertension also may affect plasma renin levels [40]. Obesity not only affects plasma renin levels [41], it also is an important risk factor for OSA [42]. Recent studies suggest that adipose tissue might function as an endocrine organ. The adipose tissue possesses functionality of several components of the RAS including angiotensin II (ANG II), angiotensin converting enzyme, and ANG II type I receptor [41]. These adipose-tissue-derived components release into the circulation and increase BP. In the current study, renin levels were compared in normal-weight and overweight OSA subjects. We found that renin levels in overweight children with OSA compared to overweight control subjects were not statistically significant ($P = 0.07$). In addition, plasma renin levels were not significantly different between normal-weight and overweight subjects in both control and OSA groups.

Elevated BP and hypertension are common comorbid conditions in OSA patients [43]. In the current study, we have reported for the first time an absence of normal negative associations between plasma renin level and BP in both OSA and obese children. Unlike normal-weight children without OSA, both overweight and OSA children had elevated renin levels despite having elevated BP. It is well established that increased sympathetic activity plays a critical role in increasing BP and developing hypertension in OSA. Failure to reduce renin levels with BP elevation in overweight and OSA children may be a potential mechanism of increased BP in OSA. Several factors related to OSA may contribute to dysfunction of the renin–BP relationships. Intermittent nocturnal hypoxemia and partial sleep loss are important mechanisms for increased sympathetic neural activity [44]. Elevated sympathetic drive plays a critical role in BP and renin release that might be a mechanism of loss of relationship. Indeed, intermittent hypoxia increases arterial BP in humans through the RAS-dependent mechanism [45]. Sleep fragmentation due to repeated night-time arousal also has been considered as a mechanism of neurohumoral activation, metabolic dysfunction, and consequent cardiovascular dysfunction in patients with OSA [46].

Normal sleep and sleep cycle also affect plasma renin levels [47]. Non-REM sleep is associated with increased renin level [48] and REM sleep is associated with decreased renin level [49]. The EEG activity during normal sleep and the internal sleep-architecture disorganization in patients with OSA may be associated with increased plasma renin level. However, results of the current study did not show any significant differences in sleep architecture regarding percent time spent in different sleep stages between OSA and control subjects for both normal-weight and overweight groups. In this study, blood samples for the measurement of renin were collected in the early morning after children with OSA were exposed to overnight hypoxic events and sleep disturbance. Thus, night-time hypoxia and sleep disturbances due to repeated arousals in OSA children may be a mechanism of abnormal relationships between renin level and BP.

Age, gender, and race also affect renin levels [50]. A major strength of the current case–control study is that the study protocol strictly followed predetermined criteria for selection of children with and without OSA as study subjects. Overweight and normal-weight children with OSA were matched for age, gender, race, and BMI *z*-scores to their respective control groups. BMI *z*-scores measure degree of adiposity [51], which correlated highly with direct measures of body fat. In addition, statistical adjustment was performed for age, gender, race, and diastolic BP.

The major limitation of the current study is that the pubertal status of subjects was not determined, and hormonal changes at the onset of puberty might affect BP and thus plasma renin levels. However, considering the similar ages in the OSA and control subjects for both overweight and normal-weight groups, the proportion of children in the study who had entered puberty may have been similar. In addition, the findings of our study are adjusted for age, gender, race, and diastolic BP. Therefore, significantly negative associations between plasma renin level and BP were likely not related to puberty.

In conclusion, we found that plasma renin levels are not significantly different in OSA and control subjects for both normal-weight and overweight groups. The absence of normal negative associations between renin level and BP determined for overweight and OSA subjects suggests dysfunction of the renin–BP relationship in both overweight children and children with OSA. The presence of OSA, particularly in overweight children, may be associated with dysfunction of the RAS, which could be a mechanism of increased BP and development of hypertension. Future study will determine whether treatment of OSA normalizes the relationship between plasma renin level and BP.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.022.

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